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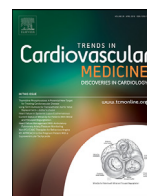
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Translational overview of cytokine inhibition in acute myocardial infarction and chronic heart failure[☆]

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ABSTRACT

Many cytokines are currently under investigation as potential target to improve cardiac function and outcome in the setting of acute myocardial infarction (MI) or chronic heart failure (HF). Here we aim to provide a translational overview of cytokine inhibiting therapies tested in experimental models and clinical studies. In various experimental studies, inhibition of interleukin-1 (IL-1), -6 (IL-6), -8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), CC- and CXC chemokines, and tumor necrosis factor- α (TNF- α) had beneficial effects on cardiac function and outcome. On the other hand, neutral or even detrimental results have been reported for some (IL-1, IL-6, IL-8, and MCP-1). Ambivalence of cytokine function, differences in study designs, treatment regimens and chosen endpoints hamper the translation of experimental research into clinical practice. Human studies are currently limited to IL-1 β inhibition, IL-1 receptor antagonists (IL-1RA), IL-6 receptor antagonists (IL-6RA) or TNF inhibition. Despite favorable effects on cardiovascular events observed in retrospective cohort studies of rheumatoid arthritis patients treated with TNF inhibition or IL-1RA, most prospective studies reported disappointing and inconsistent results. Smaller studies ($n < 100$) generally reported favorable results of anticytokine therapy on cardiac function, but only one of the larger studies ($n > 100$) evaluating IL-1 β inhibition presented positive results on outcome. In conclusion, of the 10 anticytokine therapies tested in animals models beneficial effects have been reported in at least one setting. In larger clinical studies, findings were unsatisfactory in all but one. Many anticytokine therapies with promising animal experimental data continue to require further evaluation in humans.

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Introduction

Acute myocardial infarction (MI) and chronic heart failure (HF) are associated with decreased quality of life and unfavorable long-term outcome [1–3] and novel therapeutic strategies are still needed to improve clinical outcome. After successful introduction of antiplatelet inhibitors, beta-blockers, statins, and renin-angiotensin-aldosterone inhibitors, more recently there is increasing interest to target inflammation more specifically by immunomodulation or specific anticytokine treatment.

Cardiac remodeling is one of the major contributors to progression of MI to HF and considered to be importantly mediated by inflammation [4]. Epidemiological studies suggest that circulating

concentrations of inflammatory markers, such as C-reactive protein (CRP), are associated with subsequent risk of atherosclerosis formation, coronary heart disease (CHD) and cardiac remodeling [5]. In the setting of acute MI, elevated CRP levels are associated with impaired myocardial reperfusion [6]. In principle, the inflammatory response is a protective mechanism short-term but may lead to chronic overcompensatory failure. It is a complex conjunction between innate (quick and non-specific) and adaptive (slow and specific) immune systems [4,7]. Upon tissue damage or endothelial cell stress, cardiomyocytes, leukocytes and platelets can release various inflammatory cytokines attracting antigen presenting cells. Antigen presenting cells such as dendritic cells, monocytes and macrophages from the innate immune system will recognize released self-antigens or danger signals and start to interact with B and T cells from the adaptive immune system [8,9]. This interaction may be caused by the formation of receptor complexes and via cytokine production further activates and amplifies the instigated inflammatory response. Cytokines, such as interleukin-1

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(IL-1), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor- α (TNF- α) were previously found to be elevated in MI and HF [10,11]. They are known to promote cell death of cardiomyocytes and cell hypertrophy by induction of intracellular signaling cascades such as NF- κ B, JAK/STAT and PI3K pathways in leukocytes. Some cytokines may even function as biomarker(s) while the extent of elevation has been associated with outcome and degree of cardiac injury [12,13]. Anticytokine therapy targeting inflammation is widely used and successful in rheumatoid arthritis [14] and is currently an active field of investigation for treatment of MI and HF. Since their fluctuations during the process of cardiovascular remodeling and observed associations with clinical outcome, cytokines have attracted attention as potential therapeutic targets. The aim of this review is to provide a contemporary and translational overview of potential effects of cytokine inhibition on cardiac function and outcome in the setting of acute MI and chronic HF.

Outline of this review

For the selection of clinical studies, a total of 923 articles were screened (Supplements Methods). Irrelevant articles based on article type, study design, patient population, and drug therapy were excluded. In total, 25 articles including 14 randomized clinical trials (RCTs) were reviewed thoroughly. For selection of animal experimental studies, we included search results and references of the clinical search and initially reviewed 56 articles of which 50 articles were considered relevant and are discussed. Since there are many pro-inflammatory cytokines being studied in the experimental field, we mainly focused on those that are currently under investigation in the clinical setting. An introductory overview of cytokine levels and their mechanisms in cardiovascular disease has been given in the Supplements.

Anticytokine therapy in experimental MI models

IL-1 inhibition in small animals

A variety of experimental MI models evaluated the effect of IL-1 inhibition. Pre-treatment with IL-1 receptor antagonist (IL-1RA) showed positive effects on left ventricular ejection fraction (LVEF) and infarct size in a murine ischemia reperfusion model (Fig. 1) [15]. IL-1 receptor 1 knockout mice (IL-1R1, one of the receptors of the IL-1R superfamily) undergoing permanent coronary artery ligation, had larger infarct size compared to controls [16]. This aligns well with the observation that genetically engineered rat overexpressing IL-1RA in an ischemia reperfusion model had reduced infarct size and apoptosis [17]. IL-1RA overexpression in mice undergoing permanent coronary artery ligation had an equivalent effect on cardiac function and in the infarct-remote zone collagen expression was reduced, suggesting involvement of IL-1 in cardiac fibrosis [18]. Both pre- and post-treatment with IL-1RA have been reported to exert beneficial effects on cardiac function, dimensions and infarct size after permanent coronary artery ligation and ischemia reperfusion in mice and rats. Anakinra (recombinant human IL-1RA inhibitor) treatment initiated in the first weeks after permanent coronary artery ligation also resulted in improved left ventricular (LV) dimensions and fractional shortening (FS) [19]. These findings have been replicated in a comparable study with immediate and delayed treatment of anakinra causing a reduction in infarct size [20]. IL-1 inhibition with IL-1 trap, also known as rilonacept, a long-acting IL-1 inhibiting agent, was likewise successful in a chronic MI model. Using different dosages, less apoptosis and smaller infarct size was observed and LV dimensions and FS were attenuated [21]. Moreover, specific IL-1 β inhibition after permanent coronary artery ligation led to less LV dilatation and

increased FS [22]. Interestingly, in a larger chronic MI study, detrimental effects have been reported with mice having larger infarct size, lower collagen gene expression and more ventricular ruptures after treatment with a similar dose of IL-1 β antibody [23]. Taken together, there appears to be evidence for both beneficial as well as detrimental effects of IL-1 inhibition on cardiac function and infarct size in experimental MI.

IL-6 inhibition in mice and rats

Few studies investigated the effect of activation and inhibition of interleukin-6 (IL-6) and its receptor. One study evaluated IL-6 receptor antagonist (MR16-1) or placebo treatment after permanent coronary artery ligation in mice [24]. FS increased, left ventricular end-diastolic diameter (LVEDD) was smaller and the survival rate was higher than controls. In an opposed model using gp130 knockout mice, the IL-6 binding common receptor, increased IL-6 and STAT3 expression, LV dilatation, LV rupture and mortality was seen compared to the wild-type [25]. The effect was attenuated with an additional genetic reduction of STAT3, suggesting the destructive mechanism behind gp130 impaired signaling is STAT3 dependent. Contradictory with previous studies, infarct size increased and LVEF decreased in a different study with mice treated with IL-6 monoclonal antibody prior to permanent coronary artery ligation. Neutrophil infiltration was reduced in the treatment group suggesting the inflammatory response initiated by IL-6 also has functional and cardioprotective properties [26]. In addition, treatment with IL-6/soluble IL-6 receptor (sIL-6R) complex has reduced cardiomyocyte apoptosis and lowered the infarct area vs. area at risk percentage in an ischemia reperfusion model [27]. In conclusion, with contradictory findings on its inhibition illustrated by impaired cardiac function observed after pre-treatment and opposite effects after post-treatment, IL-6 appears a difficult target for therapy.

TNF- α inhibition in small and large mammals

In various ischemia reperfusion models with TNF- α inhibitor post-treatment reduced MI size [28–30]. In an ex vivo study, treatment with monoclonal TNF- α antibodies after a period of ischemia in isolated rat hearts showed positive effects on LV pressure, coronary flow and oxygen consumption [31]. However, TNF- α blockade had no effect when tested in adiponectin knockout mice, whereas adiponectin supplementation did, suggesting the effect of TNF- α inhibition is adiponectin dependent [29]. Adiponectin itself has been shown to be cardioprotective in ischemia reperfusion and adiponectin blocks the pro-inflammatory effects of TNF- α , while elevated TNF- α can inhibit adiponectin production [29]. To the contrary, administration of low-dose TNF prior to ischemia reperfusion in isolated murine hearts resulted in reduced infarct size, suggestive of a potential preconditioning effect [32]. One chronic MI rat model receiving TNF- α inhibition post-treatment showed better LV pressures and diastolic function compared to controls [33]. In addition, less leukocyte infiltration and increased thickness of the LV free wall in the infarct area were seen. The effects of TNF- α antagonists have also been evaluated in larger mammals, including rabbits, swine, and dogs. In one rabbit study, two groups received anti-murine TNF- α sheep antibodies pre-treatment and in one group this was combined with short periods of coronary artery occlusion (ischemic preconditioning) before the main coronary artery procedure [34]. Infarct size was reduced in all treatment groups compared to controls. The concentration of circulating TNF- α correlated with infarct size. The authors suggested that ischemic preconditioning was as effective as anti-TNF- α administration in reducing infarct size. Anti-TNF- α treatment was again tested before permanent coronary artery ligation in another rabbit

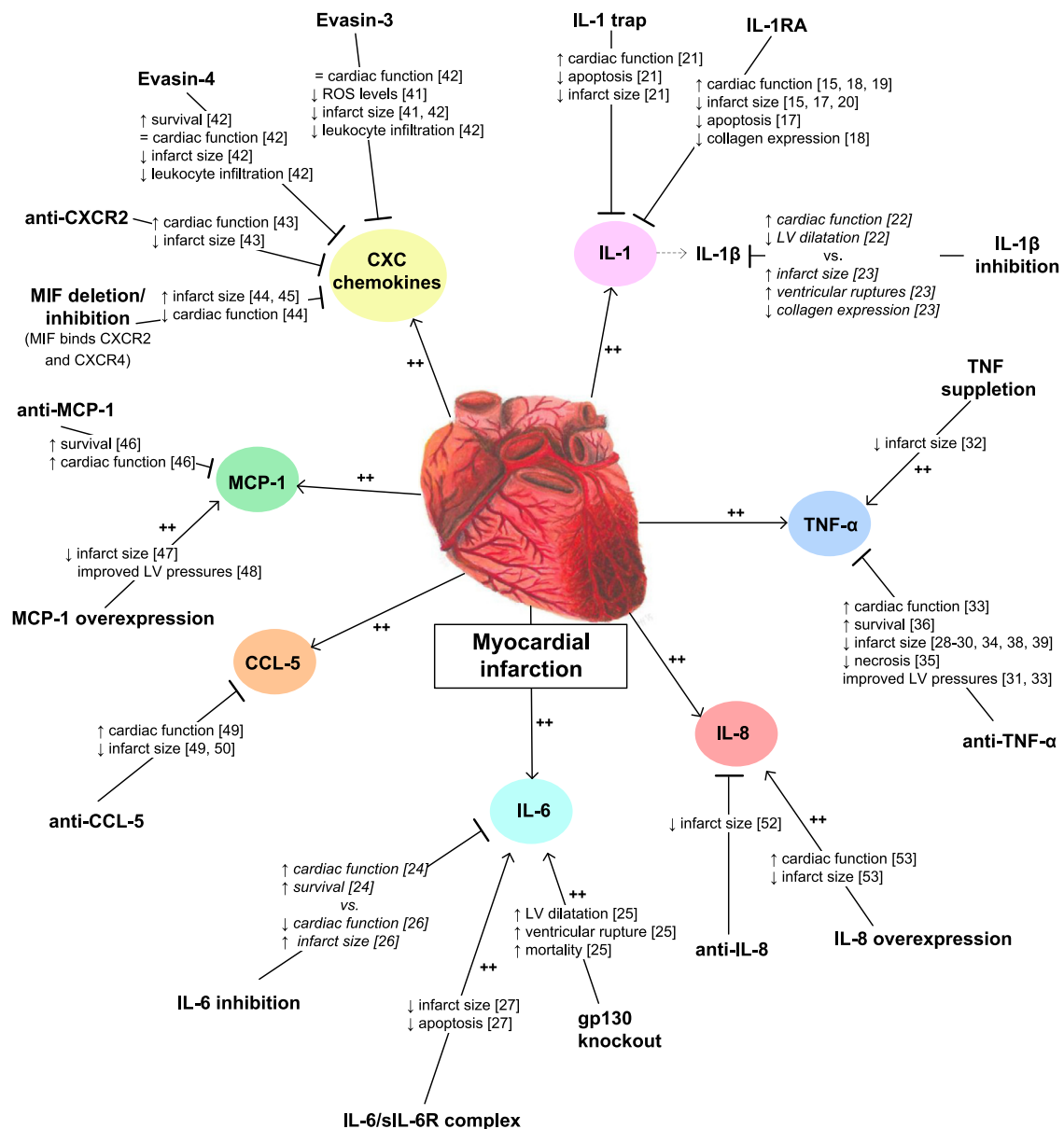


Fig. 1. Effects of cytokine supplementation, overexpression and inhibition in MI.

study and led to less necrosis, less circulating endothelial cells and neutralized levels of TNF- α compared to controls [35]. In a permanent coronary artery balloon occlusion model in swine inducing ventricular fibrillation, treatment with TNF- α inhibition resulted in survival rates almost twice as high [36]. In a similar study in swine, Infliximab treatment after induction of ventricular fibrillation and concomitant resuscitation was associated with higher mean arterial pressure and stroke work [37]. In dog ischemia reperfusion models, TNF- α inhibition after coronary artery balloon occlusion, or prior to coronary artery ligation, was associated with smaller infarct size [38,39]. Pre- and post-treatment with TNF- α antagonists in smaller and larger mammals reduced infarct size in both ischemia reperfusion and permanent myocardial ischemia models. Only two studies reported data on cardiac function after treatment with TNF- α antagonists and showed improvement of LV pressures.

CC and CXC chemokine inhibition in mice

Evasin-3 is a chemokine binding protein discovered in tick saliva. Evasin-3 binds CXCL1, CXCL8, and macrophage inflammatory

protein-2 and inhibits neutrophil cell recruitment and has been tested in experimental MI models [40]. In a model of in vivo and ex vivo coronary artery ligation lasting 30 minutes, Evasin-3 post-treatment reduced infarct size and reactive oxygen species levels [41]. The beneficial effects of post-treatment in a mouse ischemia reperfusion model were attributed to the prevention of neutrophil infiltration, which is induced by CXC chemokines. In a subsequent study, Evasin-3 and Evasin-4, chemokine binding proteins inhibiting CC chemokines (including CCL5 and CCL11), administration after inducing permanent coronary artery ligation in mice was associated with lower levels of CXCL1 and CCL2, less leukocyte infiltration and smaller infarct size [42]. The effect of Evasin-4 on circulating chemokine levels was accelerated and survival after infarction improved compared to Evasin-3. Cardiac function did not differ between Evasin-3 and -4 groups and controls. Interestingly, direct inhibition of CXCL1 and receptor CXCR2 in several regimens was not successful in mice [43]. Only anti-CXCR2 antibody improved LVEF and decreased infarct size when administered for a longer period up to 3 weeks. Inhibition of the CXCR2 and CXCR4 binding cytokine, macrophage migration inhibitory factor (MIF), was further

tested in a genetic ischemia reperfusion model with chimeric mice lacking CXCR2 and wildtype mice [44]. Pre-treatment with anti-MIF resulted in larger infarct size and impaired LVEF in wildtype mice and in the mice generated with CXCR2 lacking bone marrow derived inflammatory cells. In contrast, chimeric mice with CXCR2 lacking cardiomyocytes receiving anti-MIF treatment showed an improved LVEF compared to chimeric mice with control antibody treatment. Blocking MIF has detrimental effects presumably via CXCR2 cardiomyocytes as opposed to cardioprotective effects in CXCR2-deficient cardiomyocytes. Miller et al. [45] investigated effects of genetic deletion of MIF (MIF^{-/-}) in an ischemia reperfusion mouse model and observed larger infarct size compared to wildtype mice. In conclusion, Evasin-3 and -4 post-treatment, targeting CC and CXCR2 chemokines, were associated with smaller infarct size. CXCR2 inhibition during a longer period attenuated cardiac function in experimental MI whereas contradictory findings are reported regarding inhibition of its ligand MIF.

MCP-1 (CCL2) inhibition in mice

Anti-MCP-1 treatment in mice, administered before and after permanent coronary artery ligation, resulted in improved survival and reduced LVEDD and improved FS [46]. Extracellular matrix metalloproteinase 9 concentration, involved in collagen degradation and thereby remodeling, was lower in the anti-MCP-1 treated group. In contrast, in transgenic MCP-1 overexpressing mice infarct size was reduced in ischemia reperfusion experiments but not in permanent coronary artery ligation [47]. Likewise, in an ischemia reperfusion model with isolated hearts of MCP-1 overexpressing transgenic mice, improved LV pressures were observed [48]. Taken altogether, the effects of MCP-1 inhibition and overexpression in experimental MI are ambiguous.

CCL5 (RANTES) inhibition in mice

Several pharmacological and genetic knock-out studies have been undertaken to determine the effect of CCL5 inhibition. Mice treated with anti-CCL5 after permanent coronary artery ligation or ligation for 30 minutes resulted in improved LVEF and smaller infarct size [49]. A decline in infarct size was also observed in another ischemia reperfusion model in which mice received CCL5 antagonist prior to reperfusion [50]. On the other hand, blocking CCR5, a receptor binding CCL5 and others, in a knockout model had detrimental effects [51]. Though, CCL5 was not induced, which corresponds with the previous study suggesting CCL5 inhibition may exert its effects via CCR1 and not via de CCR5 receptor [50]. The preliminary effects of CCL5 inhibition are promising but the mechanism or receptor of action needs to be elucidated.

IL-8 inhibition in rabbits and rats

Both genetic overexpression and inhibition of interleukin-8 (IL-8) have been studied. In an ischemia reperfusion model, rabbits received a monoclonal antibody against IL-8 prior to coronary artery ligation that was associated with reduced infarct size [52]. In a chronic MI model with rats, treatment with endothelial cell transfection overexpressing IL-8 receptors at several hours after permanent coronary artery ligation decreased infarct size, inflammatory cells and improved LVEF was observed [53]. Thus far, experimental MI studies are contradictory on the effect of IL-8 inhibition and overexpression.

Anticytokine therapy in MI in humans

IL-1 inhibition

The recombinant human IL-1RA (anakinra) is currently registered for the treatment of rheumatoid arthritis. Two pilot studies and a phase 2 study with anakinra have been performed in ST-segment elevation myocardial infarction (STEMI) patients (Table 1). In the pilot study VCU-ART, 10 patients received anakinra 100 mg/day and showed a decrease in LV end-diastolic and end-systolic volume indices, compared to placebo [54]. Details on study design and results can be found in Table 1. In a consecutive RCT, 30 STEMI patients undergoing percutaneous coronary intervention (PCI) were treated with anakinra 100 mg/day or placebo during the first 2 weeks and the primary end point, left ventricular end-systolic volume index, did not differ [55]. A meta-analysis combining the data with the previous pilot study, VCU-ART, showed a lower incidence of HF symptoms in the anakinra treated group [54]. In a further analysis including extended follow-up data of these patients, treatment was associated with decreased incidence of new-onset HF diagnoses and death [56]. In the MRC ILA Heart Study, 182 acute non-ST-segment elevation myocardial infarction (NSTEMI) patients were randomized to anakinra 100 mg/day or placebo for a period of 2 weeks [57]. No differences were found in levels of high sensitive C-reactive protein (hsCRP), Troponin or von Willebrandfactor 1 week after MI. In a later publication of the same author, it was stated that the primary endpoint, hsCRP area under the curve over first 7 days, was significantly lower [58]. Unfortunately, more major adverse cardiac events (MACE) also occurred in the IL-1RA treatment group during 1-year follow-up. In contrast, the recent CANTOS RCT including 10,061 patients with previous MI and hsCRP levels ≥ 2 mg/L showed promising results. Treatment with canakinumab, an IL-1 β targeting monoclonal antibody, resulted in a lower incidence of cardiovascular events [59]. As can be expected, fatal infection or sepsis was more prevalent in the treatment groups. Nonetheless, fatal cancer, with almost double the incidence rate, was significantly lower in the treatment groups. Although future studies are needed to evaluate the safety profile and to reaffirm these study results, canakinumab is the most promising anticytokine therapy studied in MI. The double-blind RCT VCU-ART3 in STEMI patients is currently ongoing, evaluating IL-1RA treatment on CRP [60].

TNF- α inhibition

TNF- α antagonists (infliximab, etanercept, and adalimumab) are commonly used anti-inflammatory agents and inhibit TNF- α signaling by binding to its soluble receptors sTNFR1 and sTNFR2. Only one double-blind RCT evaluated the effect of etanercept 10 mg or placebo treatment in 26 acute NSTEMI patients [61]. Etanercept reduced neutrophil and IL-6 levels, although an increase in platelet-monocyte aggregation was seen. Cardiac function and infarct size were not assessed in this study, prohibiting a hard conclusion on the effects of etanercept.

IL-6 inhibition

Promising results have recently been reported on the effect of a single dose of tocilizumab, an IL-6 receptor antagonist, on the primary endpoint hsCRP levels in NSTEMI patients (Table 1) [62]. In this double-blind trial, Area under the curves of hsCRP and Troponin T were higher in the placebo group, suggesting the inflammatory response can be attenuated by tocilizumab. Echocardiography at 6 months follow-up showed no difference in cardiac function between the groups, although the trial was not primarily powered for this endpoint.

Table 1
Cytokine inhibition in MI—randomized clinical trials.

Targeted cytokine	Main findings	N, age	Treatment	Follow-up period	Author, year
Double blind RCT on IL-1RA after STEMI	+ stable LV function, lower incidence of heart failure	30 Mean age 58.7	Anakinra 100 mg/day SC during 14 days compared to placebo treatment	14 weeks	Abbate et al., 2013 [55] VCU-ART2
Double blind RCT on IL-1RA in NSTEMI	– no difference in levels of hsCRP, Troponin and vWF, IL-6 levels lower in placebo	182 Mean age 61	Anakinra 100 mg/day SC during 14 days compared to placebo treatment	1 year	Morton and Foley, 2011 [57]
Double blind RCT on IL-1RA after STEMI	+ safe and favorably affects LV remodeling (higher LVESVI)	10 Mean age 47.8	Anakinra 100 mg/day SC during 14 days compared to placebo treatment	14 weeks	Abbate et al., 2010 [54] VCU-ART
Double blind RCT on IL-1 β after MI	++ safe and lower incidence of cardiovascular events	10,061 Mean age 61.1	Canacinumab 50 mg, 150 mg and 300 mg SC every 3 months	Median follow-up 3.7 years	Ridker et al., 2017 [59] CANTOS
Double blind RCT on IL-6RA in NSTEMI	+/- lowers hsCRP and Troponin levels, no effects on cardiac function	117 Mean age 60	Single injection of tocilizumab 280 mg compared to placebo treatment	6 months	Kleveland et al., 2016 [62]

Abbreviations: hsCRP, high-sensitive C-reactive protein; IL-1, interleukin-1; LV, left ventricular; LVESVI, left ventricular end-systolic volume index; mg, milligram; N, number; NSTEMI, non-ST-segment elevation myocardial infarction; RA, receptor antagonist; RCT, randomized clinical trial; SC, subcutaneous; STEMI, ST-segment elevation myocardial infarction; vWF, von Willebrand factor.

Anticytokine therapy in experimental HF models

IL-1 inhibition in mice

Only limited data are available on IL-1 inhibition in HF. One experimental model induced HF by injecting IL-1 β (3 μ g/kg) causing a significant reduction in FS. When IL-1RA anakinra was administered prior to this injection, LVEF and stroke volume improved in anakinra treated mice [63].

TNF- α inhibition in rats and dogs

TNF- α inhibition has been evaluated in experimental HF induced by Isoproterenol or chronic pacing or related to an animal constitution with hypertension or diabetes. In one of these experimental HF models, spontaneously hypertensive and healthy rats underwent treatment with etanercept (TNF- α inhibitor) or placebo during 12 weeks [64]. Spontaneously hypertensive rats were suggested to display an early stage of HF with increased relative wall thickness and heart weight. After 12 weeks, FS did not differ, although relative wall thickness decreased and cardiac reserve increased compared to controls. Furthermore, TNF- α expression was not affected and blood pressure was increased only in the etanercept treatment group. In healthy rats, etanercept resulted in increased levels of β -1-adrenergic receptor mRNA expression, suggesting a positive inotropic effect. These findings indicate that anti-TNF- α treatment is ineffective and may even aggravate HF. In a different HF model with diabetic rats associated with enlarged thinned left ventricles with impaired LV function, no long-term beneficial effects within the context of cardiac function and remodeling were seen with etanercept [65]. Etanercept treatment was studied yet in another HF model with isoproterenol [66]. A single injection of isoproterenol, a systemic β -adrenergic receptor agonist, is associated with myocardial damage and numerous other characteristics resembling HF [67]. FS and LV dilatation was indeed ameliorated in rats receiving etanercept. Noteworthy, not TNF- α levels, but IL-1 β levels in the left ventricle were lower in the etanercept group. In a distinct HF model, dogs were paced chronically for 4 weeks and received placebo or etanercept treatment twice a week [68]. The chronic pacing resulted in reduced LVEF and LV dilatation. LV dilatation was less severe and LVEF was partially preserved with etanercept treatment. Also, mitochondrial respira-

tory chain enzyme complexes II and V in the etanercept group were completely or partially restored. DNA fragments, Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive cells and Aldehyde levels were normalized in the etanercept group whereby an increase was seen in the placebo group. This suggested that apoptosis and mitochondrial dysfunction in this HF model was attenuated by etanercept. Due to the variety of HF models used to test the effect of anti-TNF- α , a general conclusion is hard to determine.

Anticytokine therapy in HF in humans

IL-1 inhibition in human

Few RCTs, observational and cohort studies have evaluated the effect of TNF and IL-1 inhibition in relation to HF (Tables 2 and 3). In one study, 14-day treatment with IL-1 receptor antagonist anakinra in 7 HF patients improved median peak oxygen consumption [63]. A similar treatment protocol was followed in the D-HART study, including 12 HF patients with preserved ejection fraction (HFpEF). Anakinra treatment led to improvement in peak oxygen consumption and decrease in CRP levels [69]. The subsequent RED-HART trial including 60 HF patients treated with anakinra for 12 weeks and a different study of the same author including 30 acute decompensated HF patients treated for 2 weeks showed similar results with regards to peak oxygen consumption and reduction of CRP levels [70,71]. Furthermore, the investigators of the RED-HART trial observed an improvement in LVEF with 2 week anakinra treatment, but total incidence of death or readmission for HF did not differ among the treatment groups. In a double-blind cross-over trial, 46 rheumatoid arthritis patients received 150 mg anakinra daily treatment for 30 days [72]. The echocardiographic index of LV diastolic filling pressure, longitudinal strain measurements and LVEF improved after treatment with anakinra. However, these patients were not primarily diagnosed with HF; LVEF at baseline was within normal range according to current guidelines [73] and for the remaining echocardiographic parameters normal values are not yet available. One study reported a substantial improvement of cardiac function measured a few hours after single anakinra injection in 80 coronary artery disease patients with on average decreased LVEF at baseline [74]. In conclusion, IL-1 inhibition thus far seems a successful therapy in HF. A substudy of the CANTOS trial is cur-

Table 2
Cytokine inhibition in HF—(randomized) clinical trials.

Targeted cytokine	Main findings	N, age	Treatment	Follow-up period	Author, year
RCT on IL-1RA in HF patients	–/+ improved median peak oxygen consumption in 12 weeks treatment group	60 Median age 57 and 55 (IL-1RA groups)	Injection of anakinra 100 mg daily for 2 weeks or 12 weeks or placebo for 12 weeks	24 weeks	Van Tassell et al., 2017 [70] RED-HART
Double blind RCT on IL-1RA in ADHF patients	+ reduction in CRP	30 Median age 60 (IL1RA group)	Injection of anakinra 100 mg twice daily during 3 days and once daily during following 11 days compared to placebo	14 days	Van Tassell et al., 2016 [71]
Clinical trial on IL-1RA in HF patients	–/+ improved median peak oxygen consumption	7 Mean age 48	Anakinra 100 mg/day SC during 14 days	2 weeks	Van Tassell et al., 2012 [63]
Double blind crossover RCT on IL-1RA in HFpEF patients	+ improved peak oxygen consumption, reduction in CRP	12 Median age 62	Anakinra 100 mg/day SC during 14 days or placebo treatment followed by alternative treatment	2 weeks	Van Tassell et al., 2014 [69]
Double blind (R)CT on IL-1RA in RA patients	+ increase in LV performance (E/Em, LongS and LongSRS)	46 Mean age 56	Single injection (randomized) and 30 days (non-randomized) anakinra 150 mg SC treatment compared to prednisolone treatment	1 month	Ikonomidis et al., 2011 [72]
Double blind crossover IL-1RA RCT in CAD patients with RA	+ increase in LVEF, improved LV myocardial deformation and twisting	60 Mean age 59.5	Single injection of anakinra 100 mg SC or placebo followed by the alternative treatment after 48 hours	3 hours	Ikonomidis et al., 2014 [74]
Double blind RCT on TNFi treatment in HF patients	– no benefit of etanercept on death/HF hospitalization	2048 Mean age 63.5	Etanercept 25 mg SC once, twice or three times weekly, compared to placebo treatment	24 weeks	Mann et al., 2004 [89] RENEWAL
Double blind RCT on TNFi treatment in HF patients	– no improvement, possible CHF worsening, LVEF improved with 5 mg/kg	150 Mean age 61.4	Infliximab 5 mg/kg or 10 mg/kg IV at baseline, week 2 and week 6 compared to placebo treatment	28 weeks	Chung et al., 2003 [88] ATTACH
Double blind RCT on TNFi treatment in HF patients	+ significant dose-dependent improvement in LV structure and function	47 Mean age 55.0	Etanercept 5 mg/m ² , 12 mg/m ² SC twice weekly for 3 months compared to placebo treatment	3 months	Bozkurt et al., 2001 [85]
Controlled clinical trial on TNFi in CHF patients	+ improved systemic endothelial vasodilator capacity	18 Mean age 53.6	Single dose of etanercept 25 mg SC compared to controls without treatment	1 week	Fichtlscher-er et al., 2001 [87]
Double blind RCT on TNFi treatment in HF patients	+ significant improvement of LVEF in 4 or 10 mg/m ² group	18 Mean age 63.3	Single infusion of etanercept 1, 4 or 10 mg/m ² IV or placebo treatment	2 weeks	Deswal et al., 1999 [86]

Abbreviations: ADHF, acute decompensated heart failure; CAD, coronary artery disease; CHF, congestive heart failure; CRP, C-reactive protein; E, early transmitral flow velocity; Em, early diastolic mitral annulus velocity; HF, heart failure; IV, intravenously; kg, kilogram; LongS, longitudinal end-systolic strain; LongSRS, longitudinal peak systolic strain rate; LV, left ventricular; LVEF, left ventricular ejection fraction; mg, milligram; m², square meters; N, number; RA, rheumatoid arthritis; RCT, randomized clinical trial; SC, subcutaneous; TNFi, TNF inhibitors.

Table 3

Cytokine inhibition and CVD—cohort and retrospective studies.

Targeted cytokine	Main findings	N, age	Treatment	Follow-up period	Author, year
Cohort study on TNFi in RA patients	++ modest increase in LVEF and reduced biochemical HF markers	23 Mean age 51.3	Infliximab 3 mg/kg body weight per infusion every 8 weeks	1 year	Kotyla et al., 2012 [76]
Cohort study on TNFi in RA patients and CV events	++ reduced risk of non-fatal and fatal cardiovascular events	10,156 Mean age 59	TNFi treatment in person years of exposure	Mean 22.9 months	Greenberg and Kremer, 2011 [82]
Cohort study on TNFi in RA patients and HF incidence	+ no increased risk of (worsening) HF	2757 Mean age 53.7	Infliximab, etanercept, Adalimumab treatment compared to conventional DMARD treatment (<i>n</i> = 1491)	3 years	Listing et al., 2008 [79]
Cohort study on TNFi in elderly RA patients and HF incidence	– increased risk HF hospitalization and exacerbation, TNFi treated patients had more severe RA	1002 Mean age 73/77 in HF	At least one prescription of etanercept, infliximab and adalimumab compared to MTX using controls (<i>n</i> = 5593)	Mean 1.6/1.7 years in HF	Setoguchi et al., 2008 [80]
Cohort study on TNFi and MI incidence in RA patients	–/+ no difference in MI incidence, but reduced incidence of MI in responders	10,829 Mean age 56.8	TNFi treatment of minimal 6 months (<i>n</i> = 8659) compared to DMARD treatment (<i>n</i> = 2170)	Mean 18 months	Dixon et al., 2007 [106]
Retrospective study TNFi and exacerbation of CHF	– no difference between CHF, but mortality rates non-significantly different	103 Mean age 58.7	At least one dose of infliximab, adalimumab or etanercept compared to RA and non-RA controls (<i>n</i> = 200)	max. 4 years	Cole et al., 2007 [77]
Retrospective study on TNFi and prevalence of HF in RA/CD patients	–/+ no significant increase in HF incidence	4018 Mean age RA 40/ 38	At least three prescriptions for etanercept or infliximab compared to controls	15/21 months	Curtis et al., 2007 [78].
Retrospective study on TNFi in RA patients and CVD risk	+ risk of CVD lower in TNF blocker treated RA patients	983 Mean age 58	TNFi treatment (<i>n</i> = 531) compared to no TNFi treatment patients (<i>n</i> = 543)	max. 2 years	Jacobsson et al., 2005 [84]
Cohort study on TNFi in RA patients and HF incidence	+ HF less common in TNFi treated RA patients	13,171 Mean age 61	Infliximab or etanercept treatment compared to no TNFi treated controls	2 years	Wolfe and Michaud, 2004 [83]

Abbreviations: CD, Crohn's disease; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; DMARD, disease-modifying antirheumatic drugs; HF, heart failure; kg, kilogram; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MTX, Methotrexate; mg, milligram; N, number; RA, rheumatoid arthritis; RCT, randomized clinical trial; TNFi, TNF inhibitors.

rently evaluating improvement of peak oxygen consumption at 3 months after canakinumab in a selected group of patients with prior MI, elevated hsCRP, reduced LVEF and symptomatic HF [75].

TNF- α inhibition in human

Few small and larger cohort studies have focused on the potential beneficial effect of TNF inhibition on cardiac function and cardiovascular endpoints. In one of these cohort studies, 23 female rheumatoid arthritis patients without overt or latent history of HF underwent infliximab treatment for 1 year and LVEF increased significantly [76]. As mean LVEF was still within the normal range, it may be premature to extrapolate these results to clinical overt HF. In an observational study of 303 rheumatoid patients and controls, no difference was found in mortality and the incidence or worsening of HF [77]. Results from a larger observational study in 4018 rheumatoid arthritis and Crohn's disease patients were also neutral. The risk for HF was non-significantly increased in patients receiving TNF inhibition compared to non-biologicals [78]. In a similar neutral study, 2757 rheumatoid arthritis patients receiving either infliximab, etanercept or adalimumab were compared to 1491 patients receiving non-biological disease-modifying drugs (DMARDs) regarding the incidence or worsening of HF [79]. When corrected for cardiovascular disease (CVD) risk factors, increased incidence of HF was mainly related to disease activity scores. There was no significant risk related to TNF inhibition. The authors suggested that anti-TNF- α treatment is more

beneficial than harmful in the context of risk of HF. One study reported negative effects of TNF inhibition on HF hospitalizations in 1002 rheumatoid arthritis elderly patients compared to 5593 methotrexate users [80]. Baseline characteristics of TNF inhibitory vs. methotrexate users showed that patients taking TNF inhibitory drugs had more severe rheumatoid arthritis, indicated by higher CRP levels, more co-medication or injections and more comorbidities, though statistical significance was not reported. In addition, the study was not randomized and selection bias in TNF inhibitory drug prescription reserved to patients with more severe disease could have influenced the results. Methotrexate may also be a sub-optimal control treatment as it is reported to reduce incidence of cardiovascular events [81]. In a cohort study of Dixon et al., the incidence of MI was reduced in responders to TNF inhibitory treatment. In addition, in one of the larger cohort studies in 10,156 rheumatoid arthritis patients, the risk of non-fatal (MI) and fatal cardiovascular events was lower in the TNF inhibition group compared to patients taking DMARDs [82]. Positive effects were also observed in a study including 13,171 rheumatoid arthritis and 2568 osteoarthritis patients and in a smaller cohort showing a lower HF prevalence in TNF inhibitory drug treated patients [83,84]. When pre-existing CVD was absent, there was a low risk of HF unrelated to TNF inhibitory therapy. However, age, sex and comorbidity differed significantly between the TNF inhibitory drug and non-TNF inhibitory drug-treated groups so it remains to be determined if TNF inhibition lowers the risk for HF in these patients.

A RCT including 47 HF patients for safety and tolerability of etanercept showed LVEF improvement in a dose-dependent manner [85]. In a similar double-blind RCT including 18 HF patients, a single intravenous injection of etanercept was associated with improvement of LVEF [86] and in a different set of 18 congestive HF patients, etanercept improved endothelial vasodilator capacity [87]. In another RCT, 150 patients with HF NYHA class III–IV and LVEF \leq 35% received placebo or infliximab treatment 5 mg/kg or 10 mg/kg at baseline, week 2 and week 6 [88]. LVEF increased in the 5 mg/kg infliximab group, but the primary endpoint, clinical functional status after 2 weeks, did not improve. Conversely, 10 mg/kg infliximab treatment was associated with increased risk for HF hospitalization or death of any cause at 28 weeks.

To evaluate the effect of etanercept on HF hospitalization and death, data were combined of two RCTs; RECOVER and RENAISSANCE, including 1366 HF patients receiving placebo or etanercept 25 mg once, twice or three times a week [89]. Both studies were prematurely stopped because of a lack of benefit. Etanercept treatment did not reduce mortality or HF hospitalizations. The results did not change after subgroup analyses for NYHA class or LVEF.

In smaller RCTs, TNF- α antagonists ameliorated cardiac function. However, this positive effect is absent in previously mentioned large RCTs. In high dose, TNF- α antagonists seem to have adverse effects on clinical outcome. To summarize, TNF- α inhibition in HF patients did improve cardiac function in several smaller studies and is more likely to have a beneficial effect on cardiovascular events in patients with rheumatoid arthritis, but has failed to have such an effect in large RCTs. There are currently no large studies ongoing that evaluate TNF- α inhibition treatment in HF.

Discussion

In a wide range of experimental animal models of MI and in various HF models, cytokine inhibition has shown promising results. Few clinical studies investigated the effects of anticytokine therapy in MI and HF patients. Larger clinical trials to date have failed to show an improvement on cardiac function and outcome, except the CANTOS trial, with less cardiovascular events in MI patients treated with canakinumab. Several explanations are possible to explain this failure of translation from animal studies to human trials. First of all, the association of cytokines with MI and HF is not completely elucidated. The time course of cytokine activation and elevation may appear obvious at first glance; however it is not clear whether, for instance, the duration of ischemia and the degree of successful reperfusion (or co-medication) has an impact on the inter- and intra-individual biochemical curves of cytokine levels. The complex pathways underlying cytokine activation and interactions are still only partly understood. The presence of potential negative feedback loops correcting hormone imbalances, such as SOCS3 inhibiting IL-6 [90], are not yet clarified for most cytokines involved in MI and HF and its presence and function are not readily translatable from animals to humans [91]. Furthermore, inhibition of some cytokines may lead to increased expression of other cytokines [64]. When looking at effects of anticytokine therapy, levels of related cytokines should therefore also be taken into account.

Another complexity is that many cytokines appear to have an ambivalent role. The function and effects of cytokine activation could be time-dependent, as is contemplated for instance for IL-6 [92]. Prolonged activation and excessive cytokine production may be detrimental. Pro-inflammatory effects are counterbalanced by anti-inflammatory downstream signaling, as in the case of TNF- α [93,94], and selective inhibition of pro-inflammatory pathways is therefore challenging. In addition, other agents not discussed in this review, such as rapamycin, an immunosuppressive agent inhibiting mammalian target of rapamycin (mTOR), could have a

key position in the inflammatory chain reaction. Rapamycin is supposed to have anti-atherosclerotic effects and inhibits different cytokines, including MCP-1 [95,96]. Further studies are needed to evaluate the potential therapeutic value of rapamycin and other agents involved in the inflammatory cascade in patients with MI and HF.

At times, effects of anticytokine therapy and cytokine overexpression were in disagreement. Both anti-MCP-1 treatment [46] and MCP-1 overexpression [47] showed positive effects on cardiac function. Ischemia reperfusion and permanent coronary artery ligation models might have different effects on cytokine signaling. Lower cytokine levels have been reported in mice undergoing ischemia reperfusion vs. permanent coronary artery ligation [97]. Hypothetically, when reperfusion is achieved, the cytokine burst is interrupted together with the initial inflammatory response that is associated with beneficial effects on myocardial healing [98]. Therefore, cytokine overexpression might have a place in ischemia reperfusion, whereas anticytokine treatment is more sensible in chronic MI models. Pre-treatment could also downregulate cytokine receptors and after a second stimulation caused by infarction cardiomyocytes may be less prone to cytokine activation. Yet, in the later phase after MI, the CANTOS trial showed that a selected group of MI patients with increased inflammatory response did benefit from the IL-1 β antibody canakinumab. In a previous study in diabetes patients, canakinumab reduced inflammatory markers IL-6 and hsCRP, without an effect on LDL-cholesterol [59]. These studies together endorse the hypothesis that inhibition of inflammation prevents atherothrombosis, without a major influence on other factors involved in this process, such as cholesterol. In contrast to other studies, the CANTOS trial only included patients with elevated levels of the inflammatory marker hsCRP. It makes sense that in order to be effective the target inflammatory cytokine(s) of a particular drug should be elevated in the first place. To which extent the >20% current smokers in the CANTOS trial might explain the persistent pro-inflammatory response and if canakinumab has additional positive effects on top of quitting smoking in these patients remains unknown.

In some of the studies described, inhibition of cytokines or its receptors had contradictory consequences and interacting pathways involved in inhibition of each cytokine are as yet not cleared up. This prohibits making a general conclusion on the responsible targets and potential clinical use of anticytokine therapy. Different treatment regimens are practiced. In experimental MI mode, timing and duration of treatment vary widely. This is illustrated by a model where mice received anti-MCP-1 gene therapy 3 days before and 14 days after coronary artery ligation [46]. Effective plasma concentrations of the MCP-1 receptor binding protein are reached for 14 days after the injection, explaining the choice for this treatment regimen. Instead of long-lasting treatment, others focused on pre-treatment [15], or short-term post-treatment [28]. After initial inflammatory response in MI, a second cytokine burst has been observed after 8 days [98]. Hence, the optimal timepoint to interfere with pro-inflammatory effects of cytokines might also be after the first week, which is barely studied in the discussed experimental MI models.

Other explanations for observed discrepancies in MI models may be the different design, namely ischemia reperfusion vs. permanent coronary artery ligation. Ischemia reperfusion is believed to trigger a more pronounced inflammatory response [99]. For instance, contradictory findings have been reported for IL-6 and IL-8 inhibition. In addition, anti-inflammatory properties have been ascribed to IL-8 [100]. Hypothetically, anti-inflammatory actions by IL-6R inhibition and IL-8 overexpression may have positive effects on cardiac function during chronic MI while the opposite is true during ischemia reperfusion. Again, in experimental HF, a wide variety of models was used. In one study, HF was induced by inject-

ing IL-1 β and at the same time IL-1RA was administered [63]. As HF is a complicated disease with many underlying factors, it may be too simplistic to imitate and evaluate treatment in a model with addition and inhibition of a single cytokine. The dog model with chronic overpacing [68] might be a good model for HF caused by atrium fibrillation, but may not account for other etiologies linked to HF. Recently, guidelines have been proposed to enhance similarity of experimental animal studies and human HF and might help in providing a structured approach for translation to humans [101].

Chosen endpoints in experimental MI and HF were also disparate. In experimental models, applied methods and timing of the evaluation of the inflammatory response and cardiac remodeling were very different. To illustrate, in an ischemia reperfusion model, the inflammatory response was studied and TNF- α , IL-1 β , and IL-6 were markedly upregulated 6 hours after MI [102]. The authors of this study endorsed the assessment of inflammatory mediators to be performed during the first 3 days. They also recommended that assessment of dilatative remodeling should take place at least 4 weeks after MI. LV dilatation increased significantly between 1 and 4 weeks after MI reflecting progressive LV remodeling. In many of the previous experimental models, these criteria for measuring LV dilatation at a later time point are not met.

Again, chosen endpoints in clinical MI and HF studies differ from each other and from experimental endpoints. This makes it even harder to judge if experimental findings can be readily translated to humans. Also, publication bias in experimental studies could play a part in the neutral results found in humans. In the European Society of Cardiology guidelines, LVEF is stated as an important prognostic parameter after MI [103]. However, surrogate endpoints, including LVEF, might not be good representatives for long-term outcome. In the reviewed experimental animal studies regarding anticytokine therapy in MI, endpoints vary widely. Apart from enzymatic and functional infarct size and LVEF, other parameters, such as LV dilatation, LV pressures, LV mass and stroke work, are used to evaluate treatment effects. In the two smaller clinical MI studies, positive effects of IL-1RA were seen on NYHA class, LV dimensions, incidence of HF and death. In one larger study, they found no effects on Troponin levels 1 week after NSTEMI and the incidence of MACE after 1-year follow-up did not differ. In HF, reduced LVEF is generally associated with worse outcome [104]. In HFpEF, important predictors of HF hospitalization and cardiovascular death were LV hypertrophy, increased pulmonary artery and LV filling pressures [105]. The reviewed experimental HF model evaluated effects of IL-1RA and TNF inhibition on LVEF, FS, LV dilatation and stroke work. Human studies on anti-TNF- α inhibition mainly focused on LVEF, NYHA class, HF hospitalizations and death.

Conclusion and future perspectives

In this review we summarize the rapidly developing field of anticytokine therapy in cardiovascular disease and highlighted the contradictory findings in experimental MI and HF compared to the neutral results in clinical studies. In various experimental studies, inhibition of IL-1, -6, -8, MCP-1, CC chemokines, CXC chemokines and TNF- α had profound beneficial effects on cardiac function and outcome. On the other hand, neutral or even detrimental results have been reported for some (IL-1, IL-6, IL-8, and MCP-1) of these cytokines. Ambivalence of cytokine function, differences in study designs, species, treatment regimens, and chosen endpoints appear to hamper the successful translation of experimental research into clinical practice. In the clinical setting, only TNF- α inhibition, IL-1RA, IL-1 β inhibition and IL-6RA have been tested so far. Promising results were seen in smaller studies, but until now only one large RCT showed positive results on outcome. Many other anticytokine therapies with encouraging animal experimental data require further evaluation in humans, but the first clinical studies

suggest this translation can be troublesome. We recommend investigators of future clinical MI and HF studies to carefully consider the intensity of treatment as well as the treatment period and monitor a set of related cytokine levels throughout and after the treatment period. Furthermore, inclusion of patients should be based on a pre-specified number of primary end-point events, such as reinfarction, incidence of HF, readmission for HF, and cardiovascular death. Widely accepted surrogate endpoints that have been shown to be strongly related to outcome and are also frequently used in experimental studies, e.g., LVEF and infarct size, may be more suited in smaller clinical trials.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tcm.2018.02.003.

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